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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/380,336	11/23/1999	JOHANNES WILLEM HOFSTRAAT	AEM2527PIUS	2490

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KNOBLE & YOSHIDA
EIGHT PENN CENTER
SUITE 1350, 1628 JOHN F KENNEDY BLVD
PHILADELPHIA, PA 19103

EXAMINER	
GABEL, GAILENE	

ART UNIT	PAPER NUMBER
1641	24

DATE MAILED: 12/12/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/380,336	HOFSTRAAT, JOHANNES WILLE	
	Examiner	Art Unit	
	Gailene R. Gabel	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 July 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Continued Prosecution Application

1. The request filed on 7/22/02 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/380,336 is acceptable and a CPA has been established. An action on the CPA follows.

Amendment Entry

2. Applicant's amendment and arguments filed 7/22/03 in Paper No. 20 is acknowledged and has been entered. Claims 1, 4-6, 8-10, and 12-14 have been amended. Claims 1-14 are pending and are under examination.

3. In light of Applicant's amendment and Rule 132 declaration by Dr. Brunner, the rejection of claims 1-14 under 35 U.S.C. 102(e) as being anticipated by Kardos et al (US Patent 6,159,686), is hereby, withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1-4, 6, 7, and 9-11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 remains vague and indefinite in reciting, "detecting the analyte using the luminescence measurement" because it is unclear how the detected luminescence measurement [used] differentially excludes unbound "*labeled* reactant or immunoreactant" in the absence of analyte since there does not appear to be a separation step to separate unbound components. Thus, it appears that the *labeled* reactant or immunoreactant would emit luminescence within the irradiation wavelength even in the absence of analyte. It is further unclear what structural and functional cooperative relationship exists between the specific binding partner of the analyte and the labeled reactant or immunoreactant so as to enable luminescence and detection of analyte upon binding of the analyte with the specific binding partner. For example, does the labeled reactant or immunoreactant "react" or bind to the analyte in the same way, i.e. simultaneously, as the specific binding partner or does the reactant or immunoreactant "react" or bind only upon binding of analyte to the binding partner. Please clarify. Alternatively, it is unclear how the luminescence measurement [used] differentially identifies the presence of analyte since the claim does not set forth any steps involved in delimiting how this use is actually practiced. Does an increase or decrease in luminescence occur in the presence of analyte to thus, provide detection of analyte.

Claim 3 recites improper Markush language in reciting, "and naphthalocyanine derivatives; phthalocyanine derivatives". Change to --naphthalocyanine derivatives; and phthalocyanine derivatives" for proper Markush language.

Claim 4 is indefinite in reciting, "can complex with" because it fails to recite a positive limitation in the claim. Does Applicant intend "complexes with".

Claim 9 is indefinite in reciting, "can detect" because it fails to recite a positive limitation in the claim. Does Applicant intend "detects".

Claim 10 remains vague and indefinite in reciting, "detecting the analyte using the luminescence measurement" because it is unclear how the detected luminescence measurement [used] differentially excludes unbound "*labeled* reactant or immunoreactant" in the absence of analyte since there does not appear to be a separation step to separate unbound components. Thus, it appears that the *labeled* reactant or immunoreactant would emit luminescence within the irradiation wavelength even in the absence of analyte. It is further unclear what structural and functional cooperative relationship exists between the specific binding partner of the analyte and the labeled reactant or immunoreactant so as to enable luminescence and detection of analyte upon binding of the analyte with the specific binding partner. For example, does the labeled reactant or immunoreactant "react" or bind to the analyte in the same way, i.e. simultaneously, as the specific binding partner or does the reactant or immunoreactant "react" or bind only upon binding of analyte to the binding partner. Please clarify. Alternatively, it is unclear how the luminescence measurement [used] differentially identifies the presence of analyte since the claim does not set forth any steps involved in delimiting how this use is actually practiced. Does an increase or decrease in luminescence occur in the presence of analyte to thus, provide detection of analyte.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 1-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wieder et al. (US 5,830,769) in view of Kardos et al (US 6,159,686) for reason of record in Paper No. 7.

Wieder et al. disclose a homogeneous assay method for detecting an analyte in a test sample wherein the sample is contacted with a lanthanide ion-ligand complex coupled with an immunoreactant and comingled with a specific binding partner and wherein interligand energy transfer takes place in the binding reaction (see columns 3-4 and 8). Wieder et al. specifically teach a lanthanide ion (rare earth metal) complexed with a ligand wherein the ligand is a member of a specific binding capable of forming a changed fluorescence chelate with the lanthanide ion (see column 4, lines 5-23). The lanthanide ion includes neodynium (Nd_{3+}) and erbium (Er_{3+}) (see column 5, lines 13-17). The ligands useful as chelate, include polyaminocarboxylic acid, pyridinedicarboxylic acid, and derivatives thereof (see column 5, line 18 to column 6, line 64). The chelate forming ligand is the site for linking to specific binding partners (biospecific groups) that specifically recognize or immunologically react with another molecular species such as antibodies and antigens, hormones and receptors etc. (see column 7, lines 51-65).

Wieder et al. further disclose a sensitizing moiety to enhance or quench the fluorescence of the chelate which includes rhodamines, fluoresceins, and phycobiliproteins (see column 9, lines 9-60).

Wieder et al. differ from the instant invention in failing to teach incorporating the compositions comprising immunoreactants, labels, and reagents in a kit format. Wieder et al. also differ from the instant invention in failing to teach an apparatus comprising a light source and detector for detecting luminescence in the 800-1600 nm range. Wieder et al. also differ in failing to disclose specific ranges of light wavelengths of excitation as required by the claimed invention for measuring luminescence from the assay mixture.

Kardos et al. disclose methods and apparatus for performing sensitive detection of analytes by contacting the sample with an immunoreactant (directly labeled analyte binding reagent, i.e. antibody) provided with a label (linked to an upconverting phosphor) and a specific binding partner for the analyte (an indirectly labeled analyte binding reagent, i.e. a primary antibody that is detected by a labeled second antibody) (see column 20, lines 54-65). The immunoreactant includes antigenic epitopes, immunoglobulin, polynucleotide, streptavidin, and protein A (see column 10, lines 34-51). Upconverting labels convert long wavelength excitation radiation, i.e. near infrared, to emitted radiation (see column 5, lines 31-39, and column 11, lines 11-25). The label comprises a lanthanide ion complexed with a ligand (chelate compound) (see column 10, lines 25-27and 30-34) and the lanthanide phosphor particles may be coated with polycarboxylic acid (see column 13, lines 5-7). The lanthanide ions include erbium and neodymium (see column 29, lines 51-53). The ligand compounds or chelates which

comprise a sensitizing moiety for use as upconverting phosphors include polyaminocarboxylic acids such as ethylenediaminetetraacetic acid (EDTA) and diethylenetriaminepentaacetic acid (DTPA)(see column 29, lines 30-40). Alternatively, the sensitizing moiety may also include upconverting organic dyes such as cyanine, phthalocyanine, rhodamine, acridine, oxazine and derivatives thereof which absorb in the 400-1000 nm region (see column 30, lines 20-49). The apparatus includes an excitation light source including near infrared (pump) laser and a suitable detector such as a photodiode (see columns 31-32). Kardos et al. disclose packaging the compositions comprising upconverting labels and reagents for use in the assay in a kit formation (see column 48, lines 27-39). In addition, Kardos et al. disclose that specific binding partners of the analyte or immunoreactants to the analyte and labels may be incorporated into a carrier particle (microspheres, microparticles, immunobeads, superparamagnetic beads, and magnetic beads).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to incorporate all the immunoreactants and labels taught by Wieder et al. into a kit format such as taught by Kardos because kit formations are conventional and well known for their recognized advantage of convenience and economy. It would have been obvious to one of ordinary skill in the art at the time of the instant invention to measure fluorescence emissions from binding reactions between analyte and binding partners in the method of Wieder using the apparatus of Kardos having a light source and detector which function within 400-1000 nm wavelength range because Wieder is generic in the type of apparatus used and Kardos suggested application of his

apparatus for inorganic upconverting labels which emit luminescence in ranges such as in the method of Wieder. One of ordinary skill in the art at the time of the instant invention would have been motivated to incorporate the detection system and requirements as taught by Kardos into the method of Wieder because Kardos specifically disclosed in column 5, lines 25-39 that his detection system enables ultrasensitive detection of upconverting lanthanide phosphors and upconverting organic dyes by eliminating background noise which is a characteristic advantage in use of upconverting labels.

Response to Arguments and Rule 132 Declaration by Dr. Brenner

6. Applicant's arguments filed 7/12/02 have been fully considered but they are not persuasive. The Rule 132 Declaration by Dr. Brenner explained the structural difference between the present invention and the teachings of Wieder et al. and Kardos et al.; however, the present invention as described by Dr. Brenner is not reflected in the recited claims.

A) Applicant and Dr. Brenner contends that the lanthanide-ligand complex employed by Wieder et al. is substantially different from the lanthanide-ligand complex employed in the present invention; thus, Wieder et al. in combination with Kardos et al. fail to provide suggestion or motivation to arrive to the claimed invention. Specifically, Applicant argues that the sensitizing moiety employed in the present invention, which absorbs in the range of 400-1000 nm, is part of or in contact with the ligand which is important since the energy transfer between the sensitizing moiety and lanthanide-

ligand complex is distance dependent and optimized for energy transfer. According to Applicant, in Wieder et al., the sensitizing moieties are added to the solution as a separate component and there is a substantial distance between the sensitizing moiety (30.6 Angstrom (Brunner's declaration in paragraph 4)) and the lanthanide-ligand complex.

In response, claim 1 only recites that lanthanide-ion and ligand complex ... *comprises* a sensitizing moiety, claim 10 only recites that the *ligand is in contact with a sensitizing moiety*, and in claim 4, that the sensitizing moieties are selected from fluorescein and rhodamine derivatives. Both of claims 1 and 10 do not appear to exclude adding the sensitizing moiety as a separate component into the complex and specifically do not exclude a distance of 30.6 Angstrom distance between the sensitizing moiety and the lanthanide-ligand complex. Accordingly, the teaching of Wieder et al. which adds the sensitizing moieties to the solution, albeit as a separate component, reads on the claims as currently recited.

B) Applicant argues, as pointed out in the Dr. Brenner declaration, that the long wavelength organic molecules disclosed in Wieder et al. such as fluorescein and rhodamine are used to quench the luminescence emitted by the lanthanide-ligand complex of Wieder et al.; thus Wieder et al. teach a totally different use of fluorescein and rhodamine from the present invention.

In response, claim 1 only recites that lanthanide-ion and ligand complex ... *comprises* a sensitizing moiety ... and measuring emitted luminescence from the

mixture, claim 10 only recites that the *ligand is in contact with a sensitizing moiety* ... and measuring emitted luminescence from the mixture, and in claim 4, that the sensitizing moieties are selected from fluorescein and rhodamine derivatives. Both of claims 1 and 10 do not appear to exclude using the sensitizing moiety, i.e. fluorescein and rhodamine, to quench luminescence emitted by the lanthanide-ligand complex of Wieder et al. and specifically do not exclude a distance of 30.6 Angstrom distance between the sensitizing moiety and the lanthanide-ligand complex. Accordingly, the teaching of Wieder et al. which uses the sensitizing moiety, albeit to quench luminescence emitted by the lanthanide-ligand complex, reads on the claims as currently recited.

C) Applicant argues that the combination of the teaching of Wieder et al. with that of Kardos et al. is inoperable; thus, there is no suggestion or motivation to combine them to arrive to the claimed invention.

In response, the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). In this case, Wieder et al. disclose a method for detecting an analyte in a test sample wherein the sample is contacted with a lanthanide ion-ligand complex coupled with an immunoreactant and comingled with a specific binding partner

and wherein interligand energy transfer takes place in the binding reaction. The lanthanide ion includes neodynium (Nd_{3+}) and erbium (Er_{3+}) and ligands used in the method include polyaminocarboxylic acid, pyridinedicarboxylic acid, and derivatives thereof. Wieder et al. further disclose a sensitizing moiety to enhance or quench the fluorescence of the chelate which includes rhodamines, fluoresceins, and phycobiliproteins. Kardos et al. is incorporated with the teaching of Wieder for the disclosure of an apparatus for performing sensitive detection of analytes labeled with inorganic upconverting phosphors comprising lanthanide ions such as erbium and neodymium and which are coated with polycarboxylic acid. The apparatus includes an excitation light source including near infrared laser and a suitable detector such as a photodiode. Thus, it would have been obvious to one of ordinary skill in the art at the time of the instant invention to measure fluorescence emissions from binding reactions between analyte and binding partners in the method of Wieder using the apparatus of Kardos having a light source and detector which function within 400-1000 nm wavelength range because Wieder is generic in the type of apparatus used and Kardos suggested application of his apparatus for inorganic upconverting labels which emit luminescence in ranges such as in the method of Wieder.

7. No claims are allowed.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gailene R. Gabel whose telephone number is (703)

305-0807. The examiner can normally be reached on Monday, Tuesday, and Thursday, 5:30 AM to 2:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long V. Le can be reached on (703) 305-3399. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 305-0169.

Gailene R. Gabel
Patent Examiner
Art Unit 1641
December 2, 2003

Christopher L. Chin

CHRISTOPHER L. CHIN
PRIMARY EXAMINER
GROUP ~~1800~~ 1641